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What effect does functional appliance treatment have on the temporomandibular joint? A systematic review with meta-analysis

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Abstract: Background: The aim of the current systematic review was to compare the radiologic effects of functional appliance Class II treatment compared to no treatment on the temporomandibular joint and its components. Methods: Nine databases were searched up to June 2019 for randomized or prospective non-randomized clinical trials comparing Class II patients treated with functional appliances to untreated patients. After duplicate study selection, data extraction, and risk of bias assessment with the Cochrane tool and the ROBINS-I tool, random effects meta-analyses of mean differences (MDs) and their 95% confidence intervals (CIs) were performed, followed by the assessment of the quality of evidence with GRADE. Results: A total of 11 papers on 8 unique trials with 377 patients (39.8% male; average age 10.3 years) were finally included. Limited evidence indicated that compared to untreated growing patients functional appliance treatment was associated with increased condylar width (2 studies; MD 1.1 mm; 95% CI 0.1 to 2.2 mm; very low evidence quality), decreased anterior joint space (2 studies; MD - 0.7 mm; 95% CI - 0.5 to - 0.9 mm; very low evidence quality), increased superior joint space (2 studies; MD 0.7 mm; 95% CI 0.5 to 1.0 mm; very low evidence quality), increased posterior joint space (2 studies; MD 1.0 mm; 95% CI 0.9 to 1.2 mm; very low evidence quality), and vertical displacement of the glenoid fossa (2 studies; MD 0.4 mm; 95% CI 0.1 to 0.7 mm; very low evidence quality). The main limitations affecting the validity of the present findings were the inclusion of non-randomized studies with methodological issues, imprecision due to limited samples of the included studies, and inconsistencies among studies. Conclusions: Currently existing evidence from controlled clinical studies on humans indicates that functional appliance treatment is associated with positional and skeletal alterations of the temporomandibular joint in the short term compared to untreated controls. However, the clinical relevance of these changes remains unclear, while the quality of existing evidence is low due to methodological issues of existing studies. Review registration: PROSPERO, CRD42018109271. Keywords: Clinical trial; Functional appliance; Mandibular retrognathism; Orthodontics; Systematic review; Temporomandibular joint.

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What effect does functional appliance treatment have on the temporomandibular joint? A systematic review with meta-analysis

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Authors' contributions: The first and last authors (KSK and SNP) performed study selection, data extraction, and risk of bias assessment independently and in duplicate. Literature search and data analysis were performed from the third author (SNP). Disagreements were resolved by discussion or the involvement of the second author (TE). All authors read and approved the final manuscript.

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ABSTRACT

Background: The aim of the current systematic review was to compare the radiologic effects of functional appliance Class II treatment compared to no treatment on the temporomandibular joint and its components.

Methods: Nine databases were searched up to June 2019 for randomized or prospective non-randomized clinical trials comparing Class II patients treated with functional appliances to untreated patients. After duplicate study selection, data extraction, and risk of bias assessment with the Cochrane tool and the ROBINS-I tool, random effects meta-analyses of mean differences (MD) and their 95% confidence intervals (CIs) were performed, followed by assessment of the quality of evidence with GRADE.

Results: A total of 11 papers on 8 unique trials with 377 patients (39.8% male; average age 10.3 years) were finally included. Limited evidence indicated that compared to untreated growing patients functional appliance treatment was associated with increased condylar width (2 studies; MD 1.1 mm; 95% CI 0.1 to 2.2 mm; very low evidence quality), decreased anterior joint space (2 studies; MD -0.7 mm; 95% CI -0.5 to -0.9 mm; very low evidence quality), increased superior joint space (2 studies; MD 0.7 mm; 95% CI 0.5 to 1.0 mm; very low evidence quality), increased posterior joint space (2 studies; MD 1.0 mm; 95% CI 0.9 to 1.2 mm; very low evidence quality), and vertical displacement of the glenoid fossa (2 studies; MD 0.4 mm; 95% CI 0.1 to 0.7 mm; very low evidence quality). The main limitations affecting the validity of the present findings were the inclusion of non-randomized studies with methodological issues, imprecision due to limited samples of the included studies, and inconsistencies among studies.

Conclusions: Currently existing evidence from controlled clinical studies on humans indicates that functional appliance treatment is associated with positional and skeletal alterations of the temporomandibular joint in the short term compared to untreated controls. However, the clinical relevance of these changes remains unclear, while the quality of existing evidence is low due to methodological issues of existing studies.

Review registration: PROSPERO (CRD42017079107).

Keywords: orthodontics, mandibular retrognathism, functional appliance, temporomandibular joint, systematic review, clinical trial

MANUSCRIPT

Introduction

Functional appliances are often employed for the treatment of Class II malocclusion associated with mandibular retrusion, which have historically attempted to stimulate mandibular growth [1–2] and improve the facial profile [3].

Proof of concept for the skeletal effects of mandibular anterior repositioning with functional appliances was provided by animal studies [4–5] and early clinical studies on humans [6–9] indicating mandibular length gains and induction of condylar growth. However, evidence from subsequent well-designed clinical trials and systematic reviews thereof [10–15] indicated that the actual sagittal position of the anterior border of the mandible is only slightly affected by functional appliance treatment and Class II occlusal relationship is mostly corrected by dentoalveolar effects.

Still, there are indications that mandibular anterior repositioning and the downward / forward displacement of the condyles induces an adaptive remodeling of the condyle and the glenoid fossa [16–18] and might modify the position of the articular disc [19–20]. Clarifying the treatment-induced changes in the temporomandibular joint and its components are important in order to assess the stability of treatment-induced changes after mandibular advancement. Additionally, incidents of disc displacement after mandibular repositioning have been reported [21], even though others refute any deleterious effects on the temporomandibular joint [22].

However, the majority of existing clinical trials on this field have focused on occlusal or skeletal changes assessed through dental casts or lateral cephalograms. Robust assessments of the morphology of the skeletal / connective tissues of the temporomandibular joint necessitate imaging techniques with increased discerning ability for the joint region like Computed Tomography (CT), Cone Beam Computed Tomography (CBCT), or Magnetic Resonance Imaging (MRI) [23–26]. A previous systematic review from 2015 assessed the effect of fixed mandibular repositioning devices on TMJ morphology [27]. However, its searched covered only studies published to mid-2015, included only fixed appliances, did not factor out normal growth of the TMJ by including untreated controls, did not use the novel tool from the Cochrane Collaboration to assess the risk of bias of included non-randomized studies [28], could not perform any meta-analyses, and did not assess the quality of clinical recommendations that can be drawn from existing evidence. Therefore, it was judged that a new systematic review needed to be conducted.

Aim of the present systematic review of clinical studies was to assess the effect of functional appliance treatment on the temporomandibular joint morphology of patients with Class II malocclusion compared to untreated patients.

Material and Methods

Protocol, eligibility criteria, and registration

This review's protocol was a priori registered in PROSPERO (CRD42018109271), its literature searches transparently reported (Appendix 1), and all post hoc changes were appropriately noted (Appendix 2). This systematic review was conducted and reported according to Cochrane Handbook [28] and PRISMA statement [29], respectively.

Based on the Participants-Interventions-Comparisons-Outcome-Study design (PICOS) approach, we included randomized clinical trials or non-randomized controlled clinical trials on human adolescent patients of any age or sex with Class II malocclusion treated with removable or fixed functional appliance and skeletal condylar growth as the primary outcome. Secondary outcomes included joint space, condyle-fossa relationship, condyle-disc relationship, condyle-disc- fossa relationship, skeletal mandibular growth, disc formation, disc position. Animal studies, in vitro studies, and studies of patients with obstructive sleep apnea, juvenile idiopathic arthritis, rheumatoid arthritis, psoriasis, syndromes, fractures, surgical intervention, Class III or osteoporosis, were excluded.

Information sources and literature search

The following nine electronic databases were systematically searched for this review: MEDLINE (via PubMed), Embase, The Cochrane Library (CDSR, CENTRAL, and DARE), Virtual Health Library (including Bibliography Brazilian Dentistry and LILACS), Scopus, ISI Web of Knowledge, and ClinicalTrials.gov (Appendix 1). Manual search was applied on the databases Directory of Open Access Journals (DOAJ), Digital Dissertations (via UMI Proquest), metaRegister of Controlled Trials, WHO trials search portal, and Google Scholar for additional trials as well as for the reference lists of the included studies. The search was made without any limitations from inception of each database up to June 16th, 2019. Aside from filtering trials on humans, no other filters for language, publications year, and status were applied.

Study selection and data collection,

The identified studies from the literature search were sequentially screened by title, abstract, and full text by one author (KSK) with subsequent duplicate independent checking against the eligibility criteria by another author (SNP), while conflicts were resolved by a third author (TE).

The same protocol was applied for the extraction of study characteristics (study design, setting, country, patient number, sex, age, appliances, treatment duration, timing of follow-up, and outcome measured) and for the numerical data collection using pre-defined forms. Piloting of the forms was performed during the protocol stage until over 90% agreement was reached. When any data was missing in the trial, if possible.

Risk of bias in individual studies

The risk of bias was evaluated using the Cochrane risk of bias tool [28] for randomized trials and the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool [30] for non-randomized studies. This assessment was performed by one author (KSK) and independently checked by another author (SNP).

Data synthesis

The primary outcome of this systematic review was the change in the linear/volumetric joint space, measured as the distance/volume between the functional surface of the condyle and the articular eminence. Secondary outcomes included the anterior/posterior angle between the anterior/posterior disc band and the condylar line, the condylar coronary width, the displacement of the glenoid fossa, and the condyle's sagittal concentricity. All additional outcomes reported in included studies are also listed, but only briefly analyzed.

Data was summarized and considered suitable for pooling if similar intervention and/or control groups are compared and if similar outcomes were reported. All existing studies were included in the analysis independently of reporting completeness, if possible; where data was missing, they were calculated from existing data or requested them from the authors. For studies reporting on data before and after treatment, but not on the treatment-induced changes, we calculated those with a moderate pre-post correlation of 0.75. Mean Differences (MDs) of treatment changes for continuous outcomes and Relative Risks (RRs) for binary outcomes and their corresponding 95 % confidence intervals (CIs) were calculated. As the effects of functional appliance treatment were deemed to be highly variable according to patient age, sex, individual maturation of the maxillofacial structures, and appliance characteristics [14–15], a random-effects model was chosen to calculate the average distribution of treatment effects that can be expected [31]. A restricted maximum likelihood random-effects variance estimator was used instead of the older DerSimonian-Laird one, following recent guidance [32]. Random-effects 95% predictions were calculated for meta-analyses with at least three studies to aid in their interpretation by quantifying expected treatment effects in a future clinical setting [33].

The extend and impact of between-study heterogeneity were assessed by inspecting the forest plots and by calculating the tau-squared and the I-squared statistics, respectively. The 95% CIs (uncertainty intervals) around tau-squared and the I-squared were calculated to judge our confidence about these metrics. We arbitrarily adopted the I-squared thresholds of >75% to be considered as signs of considerable heterogeneity, but we also judged the evidence for this heterogeneity (through the uncertainty intervals) and the localization on the forest plot.

A two-tailed P-value of 0.05 was considered significant for all hypothesis-testing, except for a 0.10 used for the test of heterogeneity and reporting biases. All analyses were run in Stata SE 14.0 (StataCorp, College Station, TX) by one author (SNP) and the study's dataset was openly provided [34].

Risk of bias across studies and additional analyses

Subgroup analyses, meta-regressions, assessments of reporting biases, and sensitivity analyses were initially planned in the review's protocol but could ultimately not be conducted due to limited number of included trials (Appendix 2).

The overall quality of clinical recommendations (confidence in effects estimates) for each of the main outcomes will be rated by using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach [35] using an improved Summary of Findings table format [36]. The optimal information size was estimated for each outcome independently to be able to identify a minimal clinical important effect with an average standard deviation (based on this review's study sample), with type I and type II errors set at 5% and 20%, respectively. The minimal clinical important, large, and very large effects were conventionally defined as half, one, and two standard deviations for continuous outcomes and as relative risks of 1.5, 2.5, or 5.0 for binary outcomes [37]. This assessment of the risk of bias for among-trials was conducted independently by two authors (SNP and KSK) and discrepancies were resolved by a third author (TE).

Results

Study selection

The electronic literature yielded a total of 318 records, while 6 more were identified manually (Figure 1). After removal of duplicates and screening of titles and abstracts, 80 full texts papers were scrutinized against the eligibility criteria. After applying these eligibility criteria, a total of 11 publications pertaining to 8 unique clinical studies were finally included in this systematic review (Appendix 3).

Study characteristics

Three randomized clinical trials and 5 non-randomized comparative cohort studies were finally included, the characteristics of which can be seen in Table 1. The included studies were conducted in private practices or university clinics in six different countries (Brazil, Egypt, India, Thailand, Turkey, USA) and had been published as journal papers and/or dissertations in English or Portuguese between 1999-2018. A wide variety of removable or fixed functional appliances were used that include Activator, Bionator, Forsus Nitinol Flat-Spring, Fränkel, Herbst (combined with maxillary expansion), and Twin Block. All control groups were concurrently recruited, except from a single study that employed a historical control group from a longitudinal growth study. These six trials included a total of 377 patients treated with functional appliances or observed with an average sample size of 47 patients/study (range 18-80). Among the 7 studies reporting gender, 129/324 (39.8%) were male, while one study included only female patients. Among the 6 studies reporting age, the average patient age was 10.3 (mean ages within each study ranging between 8.5 and 11.7 years). Treatment outcome in the included studies was measurement with MRI, CT, or CBCT before and after treatment, to follow-up periods ranging from 6.0 to 18.0 months. Assessed outcome included joint space (distance or volume), condyle position or volume, disc position or concentricity, glenoid fossa position or volume, and skeletal morphology (assessed with geometric morphometrics).

Risk of bias within studies

The risk of bias of included randomized trials was high for one trial (due to detection bias) and unclear for the remaining two. It is important here to note that the vast majority of bias domains for the three included trials could not be adequately assessed, due to their poor reporting quality (Table 2a; Figure 2a). The risk of bias of all included non-randomized trials according to the ROBINS-I tool was found to be serious or critical (Table 2b; Figure 2b). The most problematic issues identified pertained to confounding, selection bias, performance bias, and detection bias.

Results of individual studies & synthesis of results

The results of all extracted outcomes from each included study trial are given in Appendix 4, filtered naively by statistical significance (at 5%) and clinically relevance (judged as having an effect at least equal to one deviation of the control group's response). Clinically relevant changes from functional appliance treatment were identified at the joint space, where shrinking of the anterior and widening of the posterior / superior joint space was seen. Insertion of the functional appliances lead to an anterior position of the condyle that was followed by a repositioning of the condyles back in their glenoid fossa after treatment. Although the condyles appeared to be seated in their fossae, the position of the condyle relative to the fossa was still anterior to its pretreatment position, while the disc was also moved more anteriorly compared to the control group. Additionally, the results of a morphometrics study [40–41] indicated that the condyle exhibited increased vertical displacement/remodeling components compared to untreated Class II controls, which was on the opposite direction of the gonion displacement/remodeling.

Quantitative pooling (meta-analyses) of at least two studies could be performed for nine outcomes: anterior joint space, posterior joint space, superior joint space, anterior angle, posterior angle, condylar coronary width, glenoid fossa sagittal displacement, glenoid fossa vertical displacement, and sagittal concentricity (Table 3; Figures 3-4). Statistically significant and clinically relevant changes in the joint space were seen after 6.0-11.0 months of functional appliance treatment, which were translated to statistically large to very large reduction in anterior joint space (2 studies; MD=-0.7 mm; 95% CI=-0.9 to -0.5 mm), increase in posterior joint space (2 studies; MD=1.0 mm; 95% CI=0.9 to 1.2 mm), and increase in superior joint space (2 studies; MD=0.7 mm; 95% CI=0.5 to 1.0 mm). These effects were fairly consistent and homogenous between studies (I^2=0%-4%). This was accompanied by a similarly consistent vertical displacement of the glenoid fossa (MD=-0.4 mm; 95% CI=-0.7 to -0.1 mm; I^2=0%), which was however of small to moderate magnitude. Finally, a statistically significant increase in condylar coronary width compared to untreated controls was seen (2 studies; MD=1.1 mm; 95% CI=0.1 to 2.2 mm), which was however of small to moderate magnitude and more heterogeneous (I^2=83%).

Risk of bias across studies, additional analyses, and quality of evidence

No formal assessment of risk of bias across studies or any subgroup / sensitivity analyses could be performed due to the limited number of included trials in the meta-analyses, which would be rendered instable by trial omissions.

The quality of evidence for all performed meta-analyses was very low according to the GRADE approach, due to the inclusion of non-randomized studies, the methodological inadequacies of included studies, imprecision of the estimated effects, and inconsistency across studies (Table 4; Appendix 5). Therefore, our confidence in the observed alterations in the TMJ associated with functional appliance treatment are hampered and future studies might change current recommendations.

Discussion

Summary of findings

This systematic review summarizes evidence from clinical studies on the effect of functional appliance Class II treatment on the temporomandibular joint. Even though functional appliances have been used for many decades to treat Class II malocclusion, only 8 clinical controlled studies with 377 were identified and found eligible for inclusion in this review.

As far as skeletal changes of the condyle or the glenoid fossa are concerned, some evidence indicated that patients treated with functional appliances differed from untreated patients. Meta-analysis of two studies indicated that the condyles of treated patients presented increased coronary width 6 to 9 months post-treatment compared to untreated controls (MD= 1.1 mm; Table 3). However, the effect was of small to moderate magnitude and close to the measurement error (Figure 3b), while the quality of evidence was very low due to bias and imprecision (Table 4). Similar findings were observed by two included studies [39, 46] that reported a small increase in condylar dimensions and volume 7 to 9 months after functional appliance treatment compared to untreated controls (Appendix 4). Interestingly, the same study found no significant increase in the volume of the glenoid fossa could be found (Appendix 4). Finally, included studies indicated that functional appliance treatment was associates with increased posterior growth of the condyles [45] and increased vertical growth of the rami [40–41] compared to untreated patients. Increased condylar growth activity after Class II treatment with functional appliances has also been confirmed in a study using single-photon emission CT [16], even though condylar growth activity was assessed only among treated patients and only in the short term.

However, positional differences for the various components of the temporomandibular joint were associated with functional appliance treatment. Meta-analysis of two studies indicated that the glenoid fossa of treated patients had been displaced more inferior 9 to 11 months post-treatment compared to untreated patients (MD=0.4 mm; Table 3), but this effect was small (Figure 3b) and supported by very low quality of evidence (Table 4). Additionally, the position of the condyle within the temporomandibular joint had also been altered through functional appliance treatment. Meta-analysis of two studies indicated that 6-9 months post-treatment, the temporomandibular joints of treated patients presented shrunken anterior joint space (MD=0.7 mm), enlarged posterior joint space (MD=1.0 mm), and enlarged superior joint space compared to untreated patients (MD=0.7; Table 3). This translates to a large to very large forward and downward movement of the condyle within the temporomandibular joint (Figure 3a), for which the quality of evidence was very low. Even though the magnitude of these effects is statistically speaking large to very large (larger than two standard deviations of the control group), their clinical relevance is debatable. This was confirmed from another two included studies: one [39] that measured anterior/posterior/superior joint space volume and one [46] that reported significant sagittal displacement of the condyle (MD=1.3 mm; Appendix 4). However, all included studies followed their patients only for a limited period ranging between 6 and 9 months (Table 4). It has been reported that although an anterior repositioning of the condyle relative to the glenoid fossa is seen in the short-term after functional appliance treatment with Herbst, one year afterwards the condyle is restored to its normal position in the glenoid fossa [22, 45] – presumably due to increased remodeling [44]. Other researchers however suggest that the use of semi-rigid functional appliances like the Forsus appliance might be preferable to rigid functional appliances like the Herbst or MARA appliance, since they former might enable better condylar repositioning post-treatment [39].

Interestingly, no consistent and significant change in the anterior or posterior angle was seen, which means that the relationship of the condylar disc to the condyle was not necessarily altered during functional appliance treatment. This was confirmed by the results of three included studies that found that functional appliance treatment did not significantly affect disc position [44], disc shape [47], or disc displacement [47]. This is in agreement with another cohort study of Class II patients treated with Herbst [22], which indicated that functional appliance treatment had a very minor positive effect, if any, on the condylar disc position. It might also be important here to note that measurement of the condylar position like the anterior and the posterior angle use as reference points the anterior and posterior limits of the disc, which are often difficult to identify on MRIs [23]. Additionally, changes in the anterior / posterior limit of the disc might not necessarily correspond to positional changes of the disc, but rather act as triggering mechanisms for adaptive activity during repositioning of the condyle, due to their anatomical connections to adjacent structures [38, 49].

As far as the performance of the used imaging modalities is concerned, MRI has been shown to be an accurate method for the assessment of soft and hard tissues of the TMJ with 95% and 93% accuracy for the identification of the disk position and osseous changes, respectively [26]. Likewise, conventional CT has been found to equally accurate in imaging of the TMJ area in terms of disk displacement identification [50]. However, other researchers report that CBCT with a voxel size of 0.125 mm is considerably more accurate in identifying osseous changes of the TMJ than MRI [51]. Compared to CBCT, MRI seems to possess low sensitivity, but good specificity [51]. However, it might be prudent for patients with a diagnosed disk pathology or deformity to also examine them with CBCT to more precisely identify any changes of the hard tissues [52]. In the present review, included studies mostly used MRI to appropriately assess disk relationships and CT or CBCT to assess the bony structures, even though the included CBCT study [46] did not report the used voxel size.

Strengths and limitations

The strengths of this systematic review consist of the registration of its a priori protocol in PROSPERO [53–54], its exhaustive literature search, its improved analytical methods [32], the use of the GRADE approach [35] to assess the quality of the meta-evidence, and the transparent provision of the study's data [34, 55].

However, certain limitations also exist. First and foremost, due to the limited studies on the field also non-randomized studies were included that are more prone to bias than randomized trials [53], had several methodological limitations [57–58], and one study included a historical control group that might introduce further bias [59]. Furthermore, the identified studies were predominantly small and this might introduce small-study effects [60]. Additionally, the observed effects were of relatively small magnitude and might not necessarily translate to clinically relevant functional TMJ differences, which was not within the scope of the present review. Finally, the limited number of included studies and their suboptimal reporting did not enable assessments of heterogeneity, as well as the conduct of several analyses for different subgroups, small-study effects, and reporting biases that were planned to assess the robustness of the analyses [61].

Conclusions

Currently existing evidence from controlled clinical studies on humans indicates that functional appliance treatment is associated with positional and skeletal alterations of the temporomandibular joint in the short term compared to untreated controls. These are mostly summarized by an anterior and inferior repositioning of the condyle, vertical displacement of the glenoid fossa, and increased condylar growth. However, the clinical relevance of these changes remains unclear, while the quality of existing evidence is low due to methodological issues of existing studies.

Abbreviations

CBCT: Cone Beam Computerized Tomography; CI: Confidence Interval; CT: Ccomputerized Tomography; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MD: Mean Difference; MRI: Magnetic Resonance Imaging; PICOS: Participants-Interventions-Comparisons-Outcome-Study design; RCT: Randomized Clinical Trial; REML: REstricted Maximum Likelihood; RR: Relative Risk; TMJ: Temporomandibular Joint.

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Table 1. Characteristics of included studies.

Study	Design; Setting; Country$	Patients (M/F); Age*	Intervention; duration#	Follow-up	Imaging method	Outcome
Arat 2001 [38]	uNRS; Uni; TUR	Cl. II/1; ANB≥4°; SN-ML 25-32° EG: 9 (2/7); 11.2 CG: 9 (4/5); 9.7	Activator; 16.0	Pre-Tx 6.0 mos post-Tx (24.0 mos)	MRI	Condyle-to-disc angle (ant/mid/post) Joint space (anterior/ posterior/ medial)
Arici 2008 [39]	RCT; Uni; TUR	Cl. II/1; OJ>5mm; Mnd RTG EG: 30 (13/17); NR CG: 30 (9/21); NR	FNFS; 7.0	Pre-Tx Post-Tx (7.0 mos)	CT	COND volume GF volume Joint space volume (anterior/ posterior)
Cevidanes 2005a;b [40–41]	RCT; Uni; USA	Cl. II/1 ≥ ¾ unit; OJ>4.5-10.0mm EG: 28 (NR); 10.3 CG: 25 (NR); 10.9	Fränkel-2; 18.0	Pre-Tx Post-Tx (18.0 mos)	MRI	PCA of skeletal morphology
Chavan 2014 [42]	uNRS; Uni; IND	Cl. II/1 EG1: 10 (6/4); 12.5 EG2: 10 (4/6); 11.5 CG: 10 (3/7); 12.0	EG1: Twin Block EG2: Bionator	Pre-Tx 6.0 mos in Tx	MRI	SAG disc concentricity SAG disc position
Chintakanon 1999; 2000 [43–44]	pNRS; pract; THA	Cl. II/1; OJ>5mm; Mnd RTG EG: 19 (14/5); 11.7 CG: 21 (13/8); 11.5	Twin Block; 6.0	Pre-Tx 6.0 mos in Tx	MRI	Condylar axial angle Coronal disk position Eminence angle SAG disc concentricity SAG disc position
Croft 1999 [45]	rNRS; pract; USA	ANB ≥4°; Cl. II ≥ ½ unit EG: 40 (16/24); 8.5 CG†: 40; NR (matched)	RME/ Herbst/ EGA; 11.0	Pre-Tx Post-Tx (11.0 mos) 2.7 yrs post-Tx	CT	Condylar growth GF displacement Joint space (anterior/ posterior/ superior)
Elfeky 2018 [46]	uNRS; Uni; EGY	Cl. II ≥ ½ unit; Mnd RTG; V-pattern EG: 22 (0/22); NR CG†: 18 (0/18); NR	Twin Block; 9.4	Pre-Tx Post-Tx (9.4 mos)	CBCT	COND position COND size GF position Joint space (anterior/ posterior/ superior/ medial)
Franco 2002; 2004 [47–48]	RCT; Uni; BRA	Cl. II/1 EG: 28 (15/13); 10.3 CG: 28 (14/14); 10.9	Fränkel-2; 18.0	Pre-Tx Post-Tx (18.0 mos)	MRI	Disc position Disc shape

CG, control group; COND, condyle; EG, experimental group; EGA, eruption guidance appliance; FA, functional appliance (unspecified); FNFS, Forsus nitinol flat-spring; GF, glenoid fossa; M, male; RCT, randomized clinical trial; Mnd RTG, mandibular retrognathism; NR, not reported; PCA, principal component analysis; pNRS, prospective non-randomized study; Pract, practice; rNRS, retrospective non-randomized study; SAG, sagittal; Uni, university; V, vertical.
# duration of active Class II treatment in months
$ countries are given with their ISO-3 code
* Age is given in years either as mean (one value) or if mean not provided as range (two values in parenthesis)
† historical

Table 2a. Risk of bias of the included randomized clinical trials with the Cochrane risk of bias tool.

Trial	Sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Arici 2008 [39]	**Unclear**- no randomization details provided information provided: “Thirty patients (17 girls, 13 boys) were randomly assigned to treatment with a fixed functional orthodontic appliance (Forsus nitinol flat -spring) for 6 to 9 months (mean, 7 months)”.	**Unclear** - no information provided.	**Unclear** - Blinding is impractical for both patients and clinician; outcome is objective, but was not assessed blindly.	**High risk** - no mention of blinding throughout the paper; blinding could have been implemented.	**Low risk** - No drop-outs or patient losses are reported.	**Unclear** - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Unclear** – No definite issue identified (except for a possible confounder of vertical skeletal configuration type)
Cevidanes 2005a;b [40–41]	**Unclear**- no randomization details provided: ” The Class II subjects were randomly allocated to 2 subgroups, treated and control, to avoid bias in the group comparison”	**Unclear** - no information provided.	**Low risk** - Blinding is impractical for both patients and clinician; outcome is objective and was assessed blindly.	**Low risk-** All images were coded and their order permutated to keep the analyst blind to subject identification group, and timing (T1 or T2).	**Low risk** - No drop-outs or patient losses are reported	**Unclear** - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Unclear** – No definite issue identified (except for a possible confounder of vertical skeletal configuration type)
Franco 2002; 2004 [47–48]	**Unclear**- no randomization details provided: “The sample was randomly dichotomized into 2 subgroups, treated subjects and untreated controls, to avoid bias in the group comparison”	**Unclear** - no information provided	**Low risk** - Blinding is impractical for both patients and clinician; outcome is objective and was assessed blindly.	**Unclear** – Blinding is mentioned: “A double-blind procedure was used”. However, no details are given and this is not mentioned at all in study published subsequently as Dissertation.	**Low risk** - No drop-outs or patient losses are reported	**Unclear** - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Unclear** – No definite issue identified (except for a possible confounder of vertical skeletal configuration type)

Table 2b. Risk of bias of the included non-randomized clinical trials with the ROBINS-I tool.

	Bias due to confounding	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall bias**
Arat 2001 [38]	Serious	No information	Low	No information	Low	Moderate	Low	Serious
Chavan 2014 [42]	Serious	Low	Low	No information	Low	Moderate	Low	Serious
Chintakanon 1999; 2000 [43–44]	Serious	Low	Low	Moderate	Low	Moderate	Low	Serious
Croft 1999 [45]	Critical	Serious	Low	Serious	Low	Moderate	Low	Critical
Elfeky 2018 [46]	Moderate	Serious	Low	No information	Moderate	Moderate	Low	Serious

Table 3. Results of random-effects meta-analyses performed.

	Treatment effects			Heterogeneity		
Outcome	**n**	**MD (95% CI)**	**P**	**tau^2 (95% CI)**	**I^2 (95% CI)**	**95% prediction**
Anterior joint space	2	-0.72 (-0.90, -0.54)	<0.001	0 (0, 2.25)	4% (0%, 99%)	NC
Posterior joint space	2	1.03 (0.87, 1.19)	<0.001	0 (0, 1.41)	0% (0%, 98%)	NC
Superior joint space	2	0.72 (0.48, 0.96)	<0.001	0 (0, 3.92)	0% (0%, 99%)	NC
Anterior angle	2	0.57 (-3.90, 5.03)	0.80	4.71 (NC)	45% (NC)	NC
Posterior angle	3	-7.28 (-16.67, 1.11)	0.09	47.61 (7.23, 921.80)	90% (7%, 99%)	-110.45, 95.90
Condylar coronary width	2	1.12 (0.06 2.19)	0.04	0.50 (0, 75.91)	83% (0%, 100%)	NC
Glenoid fossa sagittal displacement	2	-0.30 (-0.74, 0.14)	0.18	0.01 (0, 12.63)	11% (0%, 99%)	NC
Glenoid fossa vertical displacement	2	-0.39 (-0.70, -0.08)	0.01	0 (0, 5.027)	0% (0%, 99%)	NC
Sagittal concentricity	2	1.29 (-22.33, 24.91)	0.92	288.29 (NC)	99% (NC)	NC

CI, confidence interval; MD, mean difference; NC, non calculable.

Table 4. Summary of findings table according to the GRADE approach.

	Anticipated absolute effects (95% CI)				
Outcome (follow-up) Studies (patients)	**Control[a]**	**FA**	**Difference with FA**	**Quality of the evidence (GRADE)[b]**	**What happens with FAs**
Anterior joint space (6.0-9.4 mos) 54 patients (2 studies)	<0.1 mm	-	0.7 mm smaller (0.5 to 0.9 smaller)	⊕○○○ very low[c] due to bias	Might shrink anterior joint space
Posterior joint space (6.0-9.4 mos) 54 patients (2 studies)	-0.1 mm	-	1.0 mm larger (0.9 to 1.2 larger)	⊕○○○ very low[c] due to bias	Might enlarge posterior joint space
Superior joint space (6.0-9.4 mos) 54 patients (2 studies)	-0.2 mm	-	0.7 mm larger (0.5 to 1.0 larger)	⊕○○○ very low[c] due to bias	Might enlarge superior joint space
Anterior angle (6.0 mos) 58 patients (2 studies)	-0.8°	-	0.6° larger (3.9 smaller to 5.0 larger)	⊕○○○ very low[c,d] due to bias, imprecision	Little to no difference in anterior angle
Posterior angle (6.0 mos) 88 patients (3 studies)	-1.4°	-	7.3° smaller (16.7 smaller to 1.1 larger)	⊕○○○ very low[c,d] due to bias, imprecision	Little to no difference in posterior angle
Condylar coronary width (6.0-9.4 mos) 76 patients (2 studies)	-0.1 mm	-	1.1 mm wider (0.1 to 2.2 wider)	⊕○○○ very low[c,d] due to bias, imprecision	Might increase condylar coronary width
GleFo sagittal displacement (9.4-11.0 mos) 164 patients (2 studies)	-0.9 mm (posterior)	-	0.3 mm more posterior (0.7 less to 0.1 more)	⊕○○○ very low[c] due to bias	Little to no difference in glenoid fossa sagittal displacement
GleFo vertical displacement (9.4-11.0 mos) 164 patients (2 studies)	0.7 mm (superior)	-	0.4 mm more inferior (0.7 to 0.1 more)	⊕○○○ very low[c] due to bias	Little to no difference in glenoid fossa vertical displacement
Sagittal concentricity index (6.0-18.0 mos) 86 patients (2 studies)	1.3%	-	1.3% greater (22.3 smaller to 24.9 greater)	⊕○○○ very low[c,d,e] due to bias, imprecision, inconsistency	Little to no difference in sagittal concentricity

Intervention: functional appliance treatment (Activator, Bionator, Forsus Nitinol Flat-Spring, Fränkel, Herbst, Twin Block) versus control (observation) / Population: Class II adolescent patients / Setting: university clinics, private practice (Brazil, Egypt, India, Thailand, Turkey, USA).

[a] Response in the control group is based on average response of included studies.

[b] Starts from "low", due to the inclusion of randomized studies.

[c] Downgraded by one point for risk of bias (serious/critical risk of bias due to methodological limitations).

[d] Downgraded by one point due to imprecision, as the optimal information size was judged not to be met and/or the summary estimate was strewn across different categories of effect magnitude.

[e] Downgraded one for inconsistency (I^2>75%), which can affect our decision about the treatment effects.

CI, confidence interval; FA, functional appliance; GleFo, glenoid fossa; GRADE, Grading of Recommendations Assessment, Development and Evaluation; mo, month.

Figure Legends

Figure 1. PRISMA flowdiagram for identification and selection of eligible trials.

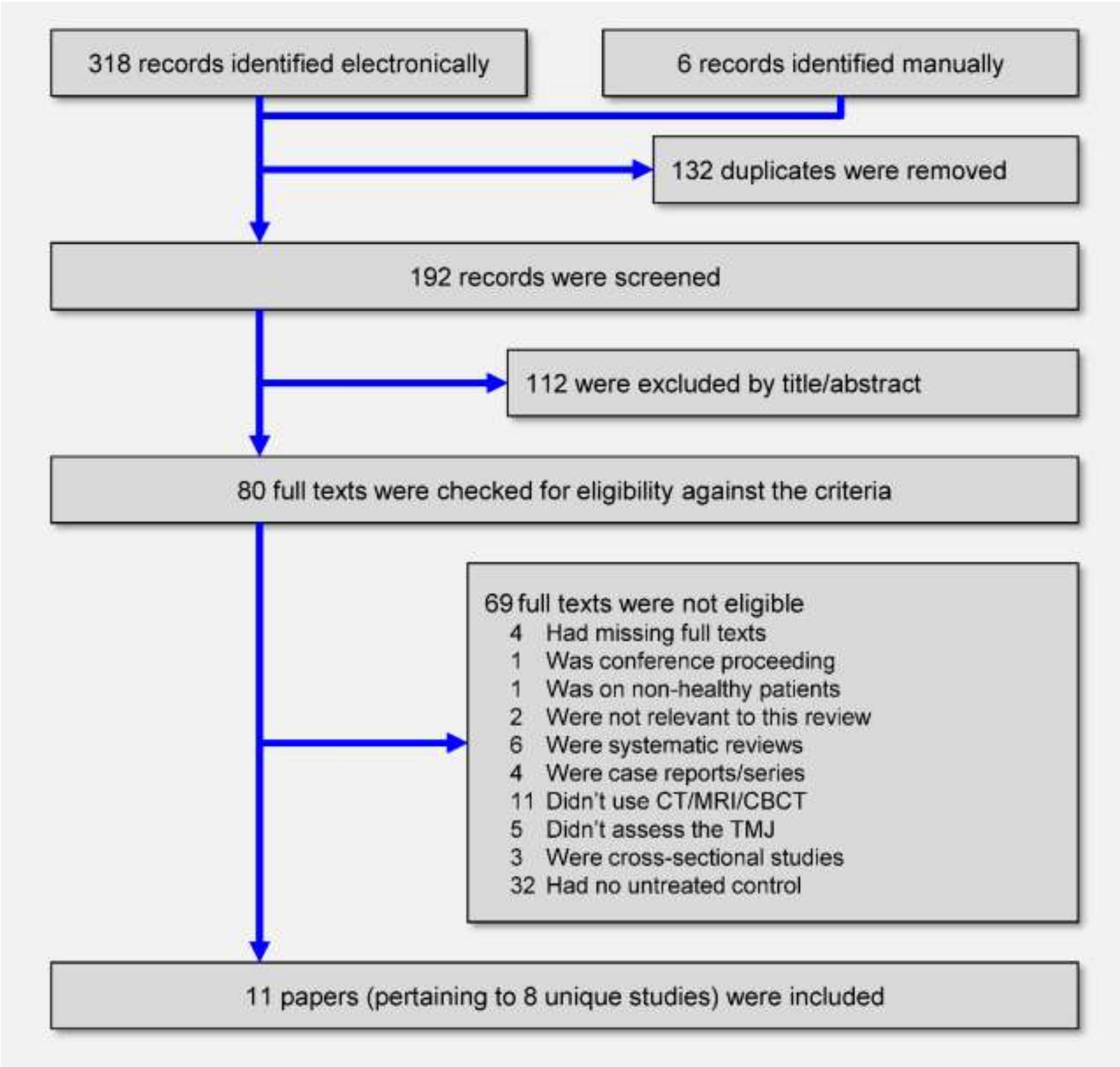


Figure 2a. Risk of bias summary for included randomized trials with the Cochrane risk of bias tool.

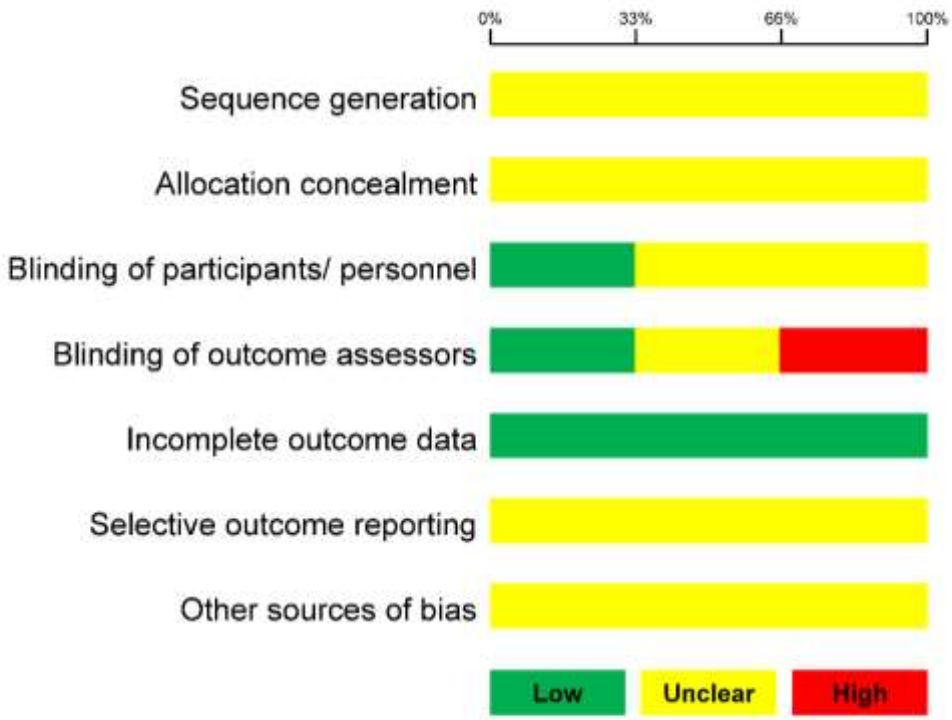


Figure 2b. Risk of bias summary for included non-randomized trials with the ROBIN-I tool.

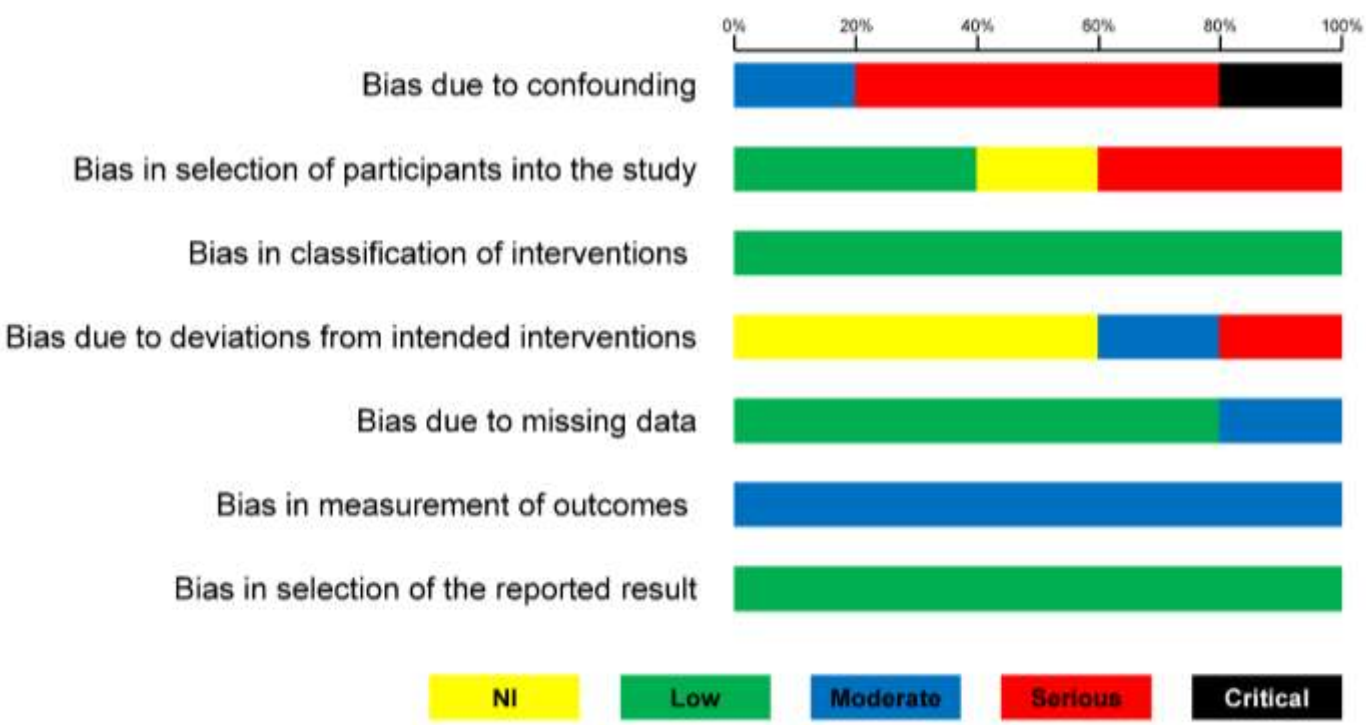


Figure 3. Contour-enhanced forest plots for random-effects meta-analyses comparing functional appliance treatment to no treatment (observation) in terms of changes in (a) anterior joint space, (b) posterior joint space, (c) superior joint space, (d) anterior angle, and (e) posterior angle.

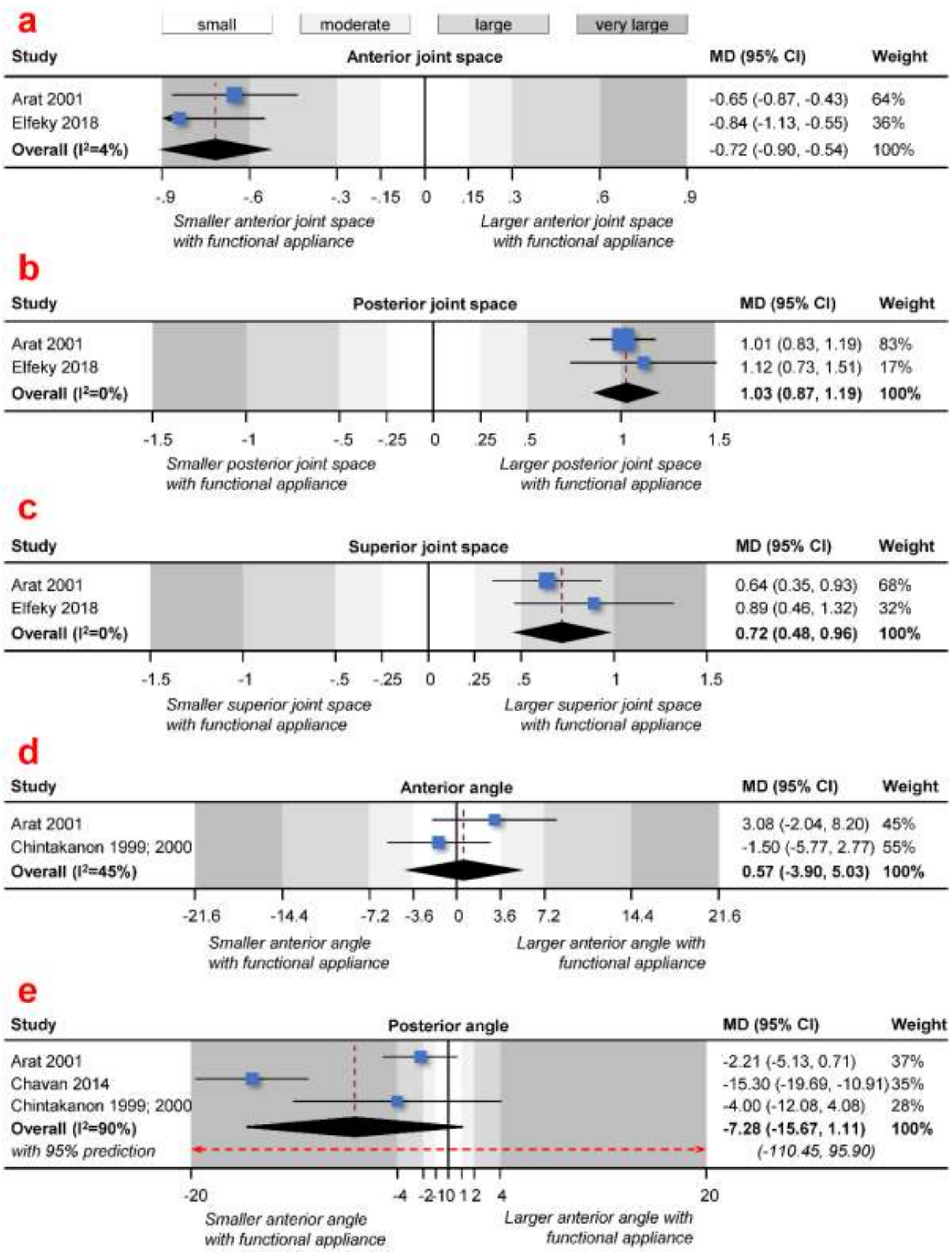
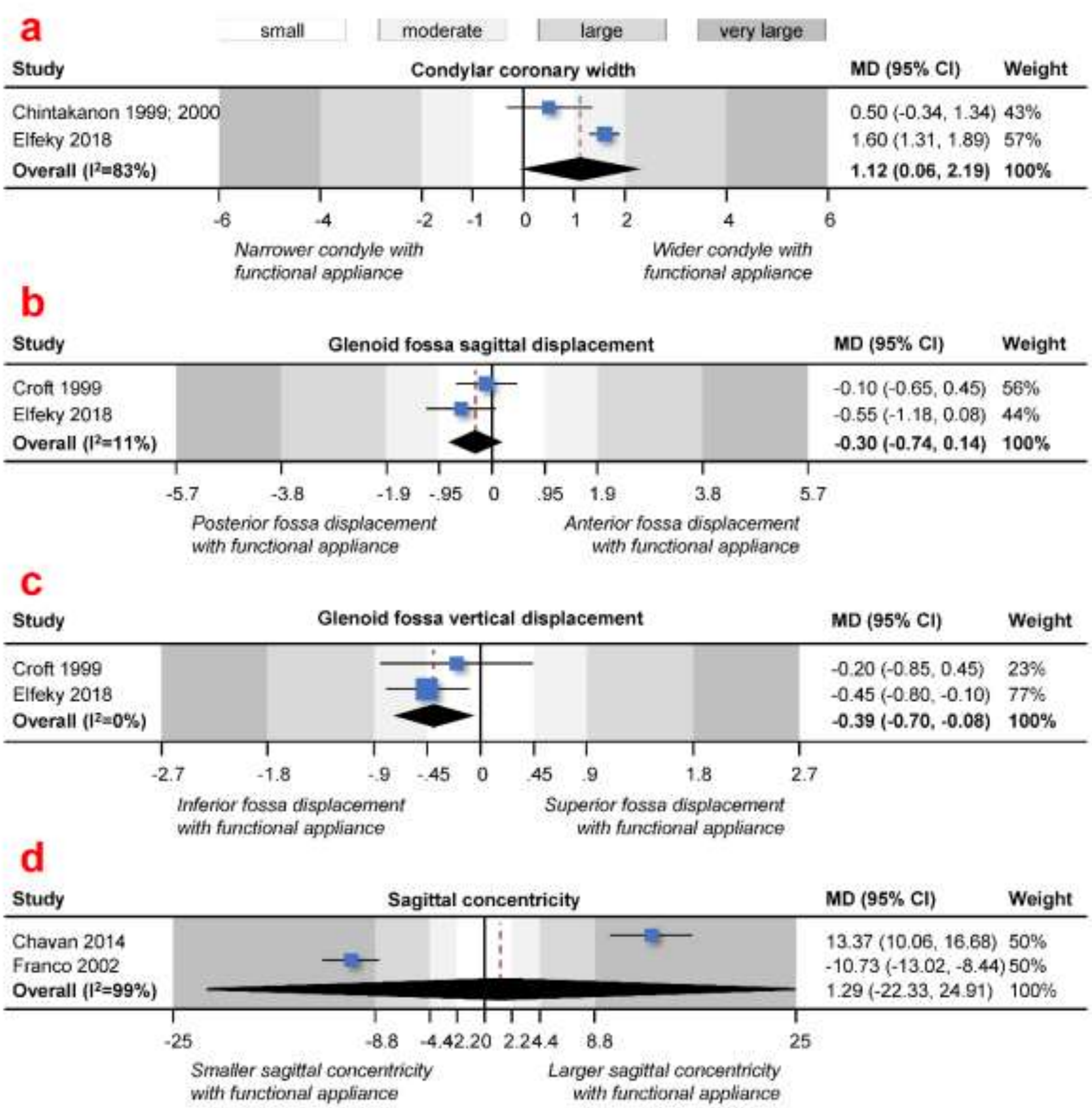


Figure 4. Contour-enhanced forest plots for random-effects meta-analyses comparing functional appliance treatment to no treatment (observation) in terms of changes in (a) condylar coronary width, (b) glenoid fossa sagittal displacement, (c) glenoid fossa vertical displacement, and(d) sagittal concentricity. CI, confidence interval; MD, mean difference.



Supplementary material

Appendix 1. Literature searched conducted to identify eligible studies (last search date June 16th, 2019).

Database	Search	Limits	Hits
MEDLINE (via Pubmed)	(orthodon* OR malocclusion OR orthopedics OR "Class II" OR prognath* OR retrognath*) AND ("functional appliance" OR "functional treatment" OR Activator OR Andresen OR Bass OR Biobloc OR Bioblock OR Bionator OR Bimler OR Crossbow OR Eureka OR Forsus OR Frankel OR Fraenkel OR Fränkel OR Harvold OR Herbst OR "Jasper Jumper" OR MARA OR "Mandibular Advancer" OR "Mandibular Anterior Repositioning" OR Monoblock OR Monobloc OR Sabbagh OR Stockli OR Stöckli OR Stoeckli OR Teuscher OR "Twin Block" OR "Twin force bite corrector") AND (TMJ OR condyle OR temporomandibular OR "mandibular joint" OR "glenoid fossa") AND ("computed tomography" OR "computer tomography" OR "cone beam" OR tomography OR CBCT OR 3D OR "mangetic resonance" OR MRI OR threedimension*)	Humans	140
Embase	Same as MEDLINE	Humans	28
Web of Knowledge	Same as MEDLINE	DENTISTRY ORAL SURGERY MEDICINE	52
Scopus	(TITLE-ABS-KEY(orthodon* OR malocclusion OR orthopedics OR "Class II" OR prognath* OR retrognath*) AND TITLE-ABS-KEY("functional appliance" OR "functional treatment" OR Activator OR Andresen OR Bass OR Biobloc OR Bioblock OR Bionator OR Bimler OR Crossbow OR Eureka OR Forsus OR Frankel OR Fraenkel OR Fränkel OR Harvold OR Herbst OR "Jasper Jumper" OR MARA OR "Mandibular Advancer" OR "Mandibular Anterior Repositioning" OR Monoblock OR Monobloc OR Sabbagh OR Stockli OR Stöckli OR Stoeckli OR Teuscher OR "Twin Block" OR "Twin force bite corrector") AND TITLE-ABS-KEY(TMJ OR condyle OR temporomandibular OR "mandibular joint" OR "glenoid fossa") AND TITLE-ABS-KEY("computed tomography" OR "computer tomography" OR "cone beam" OR tomography OR CBCT OR 3D OR "mangetic resonance" OR MRI OR threedimension*))	Dentistry	65
CDSR	Same as MEDLINE	-	0
DARE	Same as MEDLINE	-	1
CENTRAL	Same as MEDLINE	-	12
Virtual Health Library	Same as MEDLINE	-	20

Appendix 2. Additional details for this systematic review and changes from the protocol.

Deviations from protocol

- The risk of bias of included non-randomized studies was initially planned to be assessed with the Downs and Black tool that is suggested in the Cochrane Handbook. However, the ROBINS-I ("Risk Of Bias In Non-randomized Studies - of Interventions") tool has been developed in the meantime and is suggested by the Cochrane Collaboration for non-randomized studies, so we switched to this improved tool.
- The number needed to treat was planned to be calculated to clinically translate the results of meta-analyses statistically significant relative risks, but no statistically significant relative risks were ultimately found by meta-analyses.
- Possible sources of heterogeneity were planned a priori in the protocol to be sought through mixed-effects subgroup analyses and random-effects meta-regression for meta-analyses of at least five studies. This could ultimately not be assessed, as less than 5 studies were included in any meta-analysis.
- Reporting biases were planned to be assessed for meta-analyses of at least 10 studies using contour-enhanced funnel plots and with the Egger's weighted regression test. This could ultimately not be assessed, as less than 10 studies were included in any meta-analysis.
- The robustness of the results was planned to be checked a priori with sensitivity analyses based on (i) inclusion/exclusion of trials with low risk of bias and (ii) improvement of the GRADE classification. However, all results were based on one, two, or seldom three trials and therefore any trial omissions were not deemed stable.

Appendix 3. List of included/excluded studies with reasons.

Nr	Paper	Status
Excluded by title or abstract		
1	Andresen R, Radmer S, Ludtke CW, Kamusella P, Wissgott C, Schober HC. Balloon sacroplasty as a palliative pain treatment in patients with metastasis-induced bone destruction and pathological fractures. Rofo. 2014;186(9):881-6.	Excluded by title
2	Aponte-Tinao LA, Piuzzi NS, Roitman P, Farfalli GL. A High-grade Sarcoma Arising in a Patient With Recurrent Benign Giant Cell Tumor of the Proximal Tibia While Receiving Treatment With Denosumab. Clin Orthop Relat Res. 2015;473(9):3050-5.	Excluded by title
3	Arat FE, Arat ZM, Tompson B, Tanju S. Muscular and condylar response to rapid maxillary expansion. Part 3: Magnetic resonance assessment of condyle-disc relationship. Am J Orthod Dentofacial Orthop 2008;133(6):830-6.	Excluded by title
4	Aydinli U, Ozturk C, Saba D, Ersozlu S. Neglected major vessel injury after anterior spinal surgery: a case report. Spine (Phila Pa 1976). 2004;29(15):E318-20.	Excluded by title
5	Batista K, Lima T, Palomares N, Carvalho FA, Quintao C, Miguel JAM, et al. Herbst appliance with skeletal anchorage versus dental anchorage in adolescents with Class II malocclusion: study protocol for a randomised controlled trial. Trials. 2017;18(1):564.	Excluded by title
6	Behnia H, Motamedi MH, Tehranchi A. Use of activator appliances in pediatric patients treated with costochondral grafts for temporomandibular joint ankylosis: analysis of 13 cases. J Oral Maxillofac Surg. 1997;55(12):1408-14; discussion 14-6.	Excluded by title
7	Bellintani C, Ghiringhelli P, Gerloni V, Gattinara M, Farronato G, Fantini F. Temporomandibular joint involvement in juvenile idiopathic arthritis: Treatment with an orthodontic appliance. Reumatismo. 2005;57(3):201-7.	Excluded by title
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122	Ivorra-Carbonell L, Montiel-Company JM, Almerich-Silla JM, Paredes-Gallardo V, Bellot-Arcís C. Impact of functional mandibular advancement appliances on the temporomandibular joint - A systematic review. Medicina Oral, Patologia Oral y Cirugia Bucal. 2016;21(5):e565-e72.	Excluded; systematic review
123	Jimenez-Silva A, Carnevali-Arellano R, Venegas-Aguilera M, Tobar-Reyes J, Palomino-Montenegro H. Temporomandibular disorders in growing patients after treatment of class II and III malocclusion with orthopaedic appliances: a systematic review. Acta Odontologica Scandinavica. 2018;76(4):262-73.	Excluded; systematic review
124	Machado E, Grehs RA, Cunali PA. Imaging from temporomandibular joint during orthodontic treatment: a systematic review. Dental Press J Orthod. 2011 May-June;16(3):54.e1-7.	Excluded; systematic review
125	Popowich K, Nebbe B, Major PW. Effect of Herbst treatment on temporomandibular joint morphology: a systematic literature review. Am J Orthod Dentofacial Orthop. 2003;123(4):388-94.	Excluded; systematic review
126	Xinqi H, Xiao C, Jun L. [Meta-analysis of the condylar position changes produced by functional appliances in class Ⅱ malocclusion]. Hua Xi Kou Qiang Yi Xue Za Zhi. 2016 Dec 1;34(6):589-593.	Excluded; systematic review
127	Maia S, Raveli DB, Santos-Pinto Ad, Raveli TB, Gomez SP. Avaliação tomográfica no tratamento com Herbst em adulto jovem. Dental Press J Orthod. 2010;15(5):130-6.	Excluded; case report/series
128	Paulsen HU, Karle A, Bakke M, Herskind A. CT-scanning and radiographic analysis of temporomandibular joints and cephalometric analysis in a case of Herbst treatment in late puberty. Eur J Orthod. 1995;17(3):165-75.	Excluded; case report/series

129	Proff P, Richter EJ, Blens T, Fanghänel J, Hützen D, Kordaß B, et al. A Michigan-type occlusal splint with spring-loaded mandibular protrusion functionality for treatment of anterior disk dislocation with reduction. Annals of Anatomy. 2007;189(4):362-6.	Excluded; case report/series
130	Shotell MD. CBCT and Cephalometric Analysis of the TMJ Complex after Treatment Using a MARA Appliance. MSc Thesis, Loma Linda University, 2014.	Excluded; case report/series
131	Birkebaek L, Melsen B, Terp S. A laminagraphic study of the alterations in the temporo-mandibular joint following activator treatment. Eur J Orthod. 1984;6(4):257-66.	Excluded; no CT/MRI
132	Conti ACdCF, Freitas MRd, Conti PCR. Avaliação da posição condilar e disfunção temporomandibular em pacientes com má oclusão de Classe II submetidos à protrusão mandibular ortopédica. Rev Dent Press Ortod Ortop Facial (Impr). 2008;13(2):49-60.	Excluded; no CT/MRI
133	Conti ACdCF. Avaliação da posição condilar e disfunção temporomandibular em pacientes com má oclusão de classe II submetidos a protrusão mandibular ortopédica. 2004:130-.	Excluded; no CT/MRI
134	Guner DD, Ozturk Y, Sayman HB. Evaluation of the effects of functional orthopaedic treatment on temporomandibular joints with single-photon emission computerized tomography. European Journal of Orthodontics. 2003;25(1):9-12.	Excluded; no CT/MRI
135	Keeling SD, Garvan CW, King GJ, Wheeler TT, McGorray S. Temporomandibular disorders after early Class II treatment with bionators and headgears: results from a randomized controlled trial. Semin Orthod 1995;1:149–164.	Excluded; no CT/MRI
136	Lee RT, Kyi CS, Mack GJ. A controlled clinical trial of the effects of the Twin Block and Dynamax appliances on the hard and soft tissues. Eur J Orthod. 2007;29(3):272-82.	Excluded; no CT/MRI
137	Lippold C, Hoppe G, Moiseenko T, Ehmer U, Danesh G. Analysis of condylar differences in functional unilateral posterior crossbite during early treatment--a randomized clinical study. J Orofac Orthop. 2008;69(4):283-96.	Excluded; no CT/MRI
138	Nedeljković N, Glišić B, Marković E, Šćepan I, Stamenković Z. Orthodontic treatment of nongrowing patient with Class II Division 2 malocclusion by Herbst appliance. Vojnosanitetski Pregled. 2009;66(10):840-4.	Excluded; no CT/MRI
139	Santos-Pinto PRd, Martins LP, Santos-Pinto Ad, Gandini Júnior LG, Raveli DB, Santos-Pinto CCMd. Mandibular growth and dentoalveolar development in the treatment of Class II, division 1, malocclusion using Balters Bionator according to the skeletal maturation. Dental Press J Orthod. 2013;18(4):43-52.	Excluded; no CT/MRI
140	Schutz TC, Dominguez GC, Hallinan MP, Cunha TC, Tufik S. Class II correction improves nocturnal breathing in adolescents. Angle Orthod. 2011;81(2):222-8.	Excluded; no CT/MRI
141	Serbesis-Tsarudis C, Pancherz H. "Effective" TMJ and chin position changes in Class II treatment. Angle Orthodontist. 2008;78(5):813-8.	Excluded; no CT/MRI
142	Elkordy SA, Abouelezz AM, Fayed MM, Attia KH, Ishaq RA, Mostafa YA. Three-dimensional effects of the mini-implant-anchored Forsus Fatigue Resistant Device: A randomized controlled trial. Angle Orthod. 2016;86(2):292-305.	Excluded; TMJ not assessed
143	Iwasaki T, Takemoto Y, Inada E, Sato H, Saitoh I, Kakuno E, et al. Three-dimensional cone-beam computed tomography analysis of enlargement of the pharyngeal airway by the Herbst appliance. Am J Orthod Dentofacial Orthop. 2014;146(6):776-85.	Excluded; TMJ not assessed
144	Li X, Zhou HL, Lou XT, Hu Z, Shen G. [Effect of functional appliance on upper airway in adolescent patients with skeletal Class II malocclusion]. Shanghai Kou Qiang Yi Xue. 2017;26(2):222-7.	Excluded; TMJ not assessed
145	Rizk S, Kulbersh VP, Al-Qawasmi R. Changes in the oropharyngeal airway of Class II patients treated with the mandibular anterior repositioning appliance. Angle Orthod. 2016;86(6):955-61.	Excluded; TMJ not assessed
146	Schwartz JP, Raveli TB, Schwartz-Filho HO, Raveli DB. Changes in alveolar bone support induced by the Herbst appliance: a tomographic evaluation. Dental Press J Orthod. 2016;21(2):95-101.	Excluded; TMJ not assessed
147	Hansen K, Pancherz H, Petersson A. Long-term effects of the Herbst appliance on the craniomandibular system with special reference to the TMJ. Eur J Orthod. 1990;12(3):244-53.	Excluded; cross-sectional study
148	Ruf S, Pancherz H. Long-term TMJ effects of Herbst treatment: a clinical and MRI study. Am J Orthod Dentofacial Orthop. 1998;114(5):475-83.	Excluded; cross-sectional study
149	Watted N, Witt E, Kenn W. The temporomandibular joint and the disc-condyle relationship after functional orthopaedic treatment: a magnetic resonance imaging study. Eur J Orthod. 2001;23(6):683-93.	Excluded; cross-sectional study
150	Aidar LA, Abrahao M, Yamashita HK, Dominguez GC. Herbst appliance therapy and temporomandibular joint disc position: a prospective longitudinal magnetic resonance imaging study. Am J Orthod Dentofacial Orthop. 2006;129(4):486-96.	Excluded; no untreated Class II control
151	Aidar LA, Abrahao M, Yamashita HK, Dominguez GC. Morphological changes of condyles and Helkimo clinical dysfunction index in patients treated with Herbst--orthodontic appliance. Braz Dent J. 2013;24(4):313-21.	Excluded; no untreated Class II control
152	Aidar LA, Dominguez GC, Abrahao M, Yamashita HK, Vigorito JW. Effects of Herbst appliance treatment on temporomandibular joint disc position and morphology: a prospective magnetic resonance imaging study. Am J Orthod Dentofacial Orthop. 2009;136(3):412-24.	Excluded; no untreated Class II control
153	Aidar LA, Dominguez GC, Yamashita HK, Abrahao M. Changes in temporomandibular joint disc position and form following Herbst and fixed orthodontic treatment. Angle Orthod. 2010;80(5):843-52.	Excluded; no untreated Class II control
154	Aras A, Ada E, Saracoglu H, Gezer NS, Aras I. Comparison of treatments with the Forsus fatigue resistant device in relation to skeletal maturity: a cephalometric and magnetic resonance imaging study. Am J Orthod Dentofacial Orthop. 2011;140(5):616-25.	Excluded; no untreated Class II control
155	Atresh A, Cevidanes LHS, Yatabe M, Muniz L, Nguyen T, Larson B, et al. Three-dimensional treatment outcomes in Class II patients with different vertical facial patterns treated with the Herbst appliance. Am J Orthod Dentofacial Orthop 2018;154(2):238-48.e1.	Excluded; no untreated Class II control
156	Cacho A, Ono T, Kuboki T, Martin C. Changes in joint space dimension after the correction of Class II division 1 malocclusion. Eur J Orthod. 2015;37(5):467-73.	Excluded; no untreated Class II control
157	Hamilton SD, Sinclair PM, Hamilton RH. A cephalometric, tomographic, and dental cast evaluation of Frankel therapy. Am J Orthod Dentofacial Orthop. 1987;92(5):427-36.	Excluded; no untreated Class II control
158	Katsavrias EG, Voudouris JC. The treatment effect of mandibular protrusive appliances on the glenoid fossa for Class II correction. Angle Orthod. 2004;74(1):79-85.	Excluded; no untreated Class II control

159	Katsavrias EG. The effect of mandibular protrusive (activator) appliances on articular eminence morphology. Angle Orthod. 2003;73(6):647-53.	Excluded; no untreated Class II control
160	Kinzinger G, Gulden N, Roth A, Diedrich P. Disc-condyle Relationships during Class II Treatment with the Functional Mandibular Advancer (FMA). J Orofac Orthop. 2006;67(5):356-75.	Excluded; no untreated Class II control
161	Kinzinger G, Kober C, Diedrich P. Topography and morphology of the mandibular condyle during fixed functional orthopedic treatment - a magnetic resonance Imaging study. Journal of Orofacial Orthopedics-Fortschritte Der Kieferorthopadie. 2007;68(2):124-47.	Excluded; no untreated Class II control
162	Kinzinger GSM, Hourfar J, Kober C, Lisson JA. Mandibular fossa morphology during therapy with a fixed functional orthodontic appliance: A magnetic resonance imaging study. Journal of Orofacial Orthopedics. 2018;79(2):116-32.	Excluded; no untreated Class II control
163	LeCornu M, Cevidanes LH, Zhu H, Wu CD, Larson B, Nguyen T. Three-dimensional treatment outcomes in Class II patients treated with the Herbst appliance: a pilot study. Am J Orthod Dentofacial Orthop. 2013;144(6):818-30.	Excluded; no untreated Class II control
164	Lercornu M. Three dimensional treatment outcomes in class II patients treated using Herbst: a pilot study. MSc Thesis, University of North Carolina, 2013.	Excluded; no untreated Class II control
165	Liu B, Wang Y, Song F, Liu M, Duan Y, Zhou L. [Cone-beam CT evaluation of the changes in the temporomandibular joint of patients with class II division 1 subdivision malocclusion before and after twin-block treatment]. Hua Xi Kou Qiang Yi Xue Za Zhi. 2013;31(6):610-4.	Excluded; no untreated Class II control
166	Ma X, Fang B, Dai Q, Xia Y, Mao L, Jiang L. Temporomandibular joint changes after activator appliance therapy: a prospective magnetic resonance imaging study. J Craniofac Surg. 2013;24(4):1184-9.	Excluded; no untreated Class II control
167	Ma Z, Xie Q, Yang C, Zhang S, Shen Y, Cai X. Changes in the temporomandibular joint space after functional treatment of disk displacement with reduction. J Craniofac Surg. 2015;26(2):e78-81.	Excluded; no untreated Class II control
168	Pancherz H, Bjerklin K. The Herbst appliance 32 years after treatment. J Clin Orthod. 2015;49(7):442-51.	Excluded; no untreated Class II control
169	Pancherz H, Ruf S, Thomalske-Faubert C. Mandibular articular disk position changes during Herbst treatment: a prospective longitudinal MRI study. Am J Orthod Dentofacial Orthop. 1999;116(2):207-14.	Excluded; no untreated Class II control
170	Pancherz H, Sale H, Bjerklin K. Signs and symptoms of TMJ disorders in adults after adolescent Herbst therapy: a 6-year and 32-year radiographic and clinical follow-up study. Angle Orthod. 2015;85(5):735-42.	Excluded; no untreated Class II control
171	Pinto PRdS. Avaliação do crescimento mandibular e desenvolvimento dentário em crianças com má oclusão de classe II, divisão 1, naturais e induzidos pelo tratamento ortopédico com o bionator de balters. 2009:134-.	Excluded; no untreated Class II control
172	Ruf S, Pancherz H. Does bite-jumping damage the TMJ? A prospective longitudinal clinical and MRI study of Herbst patients. Angle Orthod. 2000;70(3):183-99.	Excluded; no untreated Class II control
173	Ruf S, Pancherz H. Long-term effects of Herbst treatment: A clinical and MRI study. Am J Orthod Dentofacial Orthop 1998;114(5):475-83.	Excluded; no untreated Class II control
174	Ruf S, Pancherz H. Temporomandibular joint growth adaptation in Herbst treatment: a prospective magnetic resonance imaging and cephalometric roentgenographic study. Eur J Orthod. 1998;20(4):375-88.	Excluded; no untreated Class II control
175	Ruf S, Pancherz H. Temporomandibular joint remodeling in adolescents and young adults during Herbst treatment: A prospective longitudinal magnetic resonance imaging and cephalometric radiographic investigation. Am J Orthod Dentofacial Orthop. 1999;115(6):607-18.	Excluded; no untreated Class II control
176	Ruf S, Wusten B, Pancherz H. Temporomandibular joint effects of activator treatment: a prospective longitudinal magnetic resonance imaging and clinical study. Angle Orthod. 2002;72(6):527-40.	Excluded; no untreated Class II control
177	Souki BQ, Vilefort PLC, Oliveira DD, Andrade I, Jr., Ruellas AC, Yatabe MS, et al. Three-dimensional skeletal mandibular changes associated with Herbst appliance treatment. Orthodontics and Craniofacial Research. 2017;20(2):111-8.	Excluded; no untreated Class II control
178	VanLaecken R, Martin CA, Dischinger T, Razmus T, Ngan P. Treatment effects of the edgewise Herbst appliance: a cephalometric and tomographic investigation. Am J Orthod Dentofacial Orthop. 2006;130(5):582-93.	Excluded; no untreated Class II control
179	Wadhawan N, Kumar S, Kharbanda OP, Duggal R, Sharma R. Temporomandibular joint adaptations following two-phase therapy: an MRI study. Orthod Craniofac Res. 2008;11(4):235-50.	Excluded; no untreated Class II control
180	Weiwei C, Ting S, Zhen H, Jun W. [Cone beam computed tomography analysis of the bony structure of the temporomandibular joint during two phase treatment with Herbst appliance]. Hua Xi Kou Qiang Yi Xue Za Zhi. 2016;34(5):498-501.	Excluded; no untreated Class II control
181	Yildirim E, Karacay S, Erkan M. Condylar response to functional therapy with Twin-Block as shown by cone-beam computed tomography. Angle Orthod. 2014;84(6):1018-25.	Excluded; no untreated Class II control
Included		
182	Arat ZM, Gokalp H, Erdem D, Erden I. Changes in the TMJ disc-condyle-fossa relationship following functional treatment of skeletal Class II Division 1 malocclusion: a magnetic resonance imaging study. Am J Orthod Dentofacial Orthop. 2001;119(3):316-9.	Included

183	Arici S, Akan H, Yakubov K, Arici N. Effects of fixed functional appliance treatment on the temporomandibular joint. Am J Orthod Dentofacial Orthop. 2008;133(6):809-14.	Included
184	Cevidanes LH, Franco AA, Gerig G, Proffit WR, Slice DE, Enlow DH, et al. Assessment of mandibular growth and response to orthopedic treatment with 3-dimensional magnetic resonance images. Am J Orthod Dentofacial Orthop. 2005;128(1):16-26.	Included
185	Cevidanes LH, Franco AA, Gerig G, Proffit WR, Slice DE, Enlow DH, et al. Comparison of relative mandibular growth vectors with high-resolution 3-dimensional imaging. Am J Orthod Dentofacial Orthop. 2005;128(1):27-34.	Included
186	Chavan SJ, Bhad WA, Doshi UH. Comparison of temporomandibular joint changes in Twin Block and Bionator appliance therapy: a magnetic resonance imaging study. Prog Orthod. 2014;15:57.	Included
187	Chintakanon K, Sampson W, Wilkinson T, Townsend G. A prospective study of Twin-block appliance therapy assessed by magnetic resonance imaging. Am J Orthod Dentofacial Orthop. 2000;118(5):494-504.	Included
188	Chintakanon K. A Prospective Study of Twin Block Appliance Therapy in Children with Class ll Divisionl Malocclusions Assessed by MRl, 3D-Cephalometry and Muscle Testing. Doctoral Dissertation, University of Adelaide, 1999.	Included
189	Croft RS, Buschang PH, English JD, Meyer R. A cephalometric and tomographic evaluation of Herbst treatment in the mixed dentition. Am J Orthod Dentofacial Orthop. 1999;116(4):435-43.	Included
190	Elfeky HY, Fayed MS, Alhammadi MS, Soliman SAZ, El Boghdadi DM. Three-dimensional skeletal, dentoalveolar and temporomandibular joint changes produced by Twin Block functional appliance. Journal of Orofacial Orthopedics. 2018;79(4):245-58.	Included
191	Franco AA, Yamashita HK, Lederman HM, Cevidanes LH, Proffit WR, Vigorito JW. Frankel appliance therapy and the temporomandibular disc: a prospective magnetic resonance imaging study. Am J Orthod Dentofacial Orthop. 2002;121(5):447-57.	Included
192	Franco AdA. Estudo comparativo das ATMs e das estruturas dento-esqueléticas da face, pela ressonância magnética e cefalometria radiográfica em pacientes com má oclusão de classe II divisão 1, tratados com regulador de função d Frãnkel-2 e em indivíduos com oclusão normal. 2004:[184]-[].	Included

Appendix 4. List of included studies with their analyzed outcomes.

Nr	Study	Outcome	MD	95% CI	P	SD_{CTR}	Clinically relevant
1	Chintakanon 1999; 2000	Anterior angle (FH as reference)	3.6	-1.84, 9.04	0.2	11.1	-
2	Arat 2001	Anterior angle (PC as reference)	3.08	-2.04, 8.20	0.24	4.3	-
3	Chintakanon 1999; 2000	Anterior angle (PC as reference)	-1.5	-5.77, 2.77	0.49	10.1	-
4	Arat 2001	Anterior joint space	-0.65	-0.87, -0.43	<0.001	0.2	Yes
5	Elfeky 2018*	Anterior joint space	-0.84	-1.14, -0.54	<0.001	0.48	Yes
6	Arici 2008	Anterior joint space volume	30	17.20, 42.81	<0.001	45	No
7	Arici 2008	Anterior-posterior joint space volume	46	31.05, 60.95	<0.001	67	No
8	Chintakanon 1999; 2000	Condylar axial angle	4.7	-0.97, 10.37	0.1	9.2	-
9	Elfeky 2018*	Condylar coronary AP length	0.53	0.21, 0.85	0.001	1.16	No
10	Elfeky 2018*	Condylar coronary height	1.11	0.64, 1.58	<0.001	1.36	No
11	Chintakanon 1999; 2000	Condylar coronary width	0.5	-0.34, 1.34	0.24	2.1	-
12	Elfeky 2018*	Condylar coronary width	1.6	1.31, 1.89	<0.001	1.93	No
13	Chintakanon 1999; 2000	Condylar head shape: convex	RR: 1.53	1.08, 2.18	0.02		No
14	Chintakanon 1999; 2000	Condylar head shape: flat	RR: 0.12	0.01, 2.13	0.15		-
15	Chintakanon 1999; 2000	Condylar head shape: round	RR: 0.28	0.03, 2.26	0.23		-
16	Chintakanon 1999; 2000	Condylar position: concentric	RR: 0.66	0.18, 2.41	0.53		-
17	Chintakanon 1999; 2000	Condylar position: concentric at end but not at start	RR: 0.38	0.05, 2.96	0.35		-
18	Elfeky 2018*	Condyle sagittal displacement	1.3	0.92, 1.68	<0.001	2.43	No
19	Franco 2002*	Condyle to articular tubercle	1.4	1.30, 1.50	<0.001	0.28	Yes
20	Franco 2002*	Condyle to eminence convexity change	1.19	0.84, 1.54	<0.001	0.37	Yes
21	Elfeky 2018*	Condyle transverse displacement	-0.07	-0.55, 0.41	0.78	3.04	-
22	Elfeky 2018*	Condyle vertical displacement	-0.59	-1.07, -0.11	0.02	0.86	No
23	Arici 2008	Condyle volume	11	1.16, 20.84	0.03	57	No
24	Franco 2002	Disc displacement (closed mouth)	RR: 0.20	0.01, 3.99	0.29		-
25	Franco 2002	Disc displacement (open mouth)	RR: 0.20	0.01, 3.99	0.29		-
26	Chintakanon 1999; 2000	Disc position: centric	RR: 0.66	0.18, 2.41	0.53		-
27	Chintakanon 1999; 2000	Disc position: lateral	RR: 1.24	0.60, 2.56	0.55		-
28	Chintakanon 1999; 2000	Disc position: medial	RR: 0.97	0.43, 2.16	0.94		-
29	Franco 2002	Disc shape: nonbiconcave	RR: 0.09	0.01, 1.57	0.1		-
30	Chintakanon 1999; 2000	Eminence angle (FH as reference)	-0.7	-7.58, 6.18	0.84	10.7	-
31	Chintakanon 1999; 2000	Eminence angle (PC as reference)	4.7	-2.83, 12.23	0.22	13.6	-
32	Chintakanon 1999; 2000	FH-PC angle	4.5	1.28, 7.72	0.006	9.3	No
33	Croft 1999	Glenoid fossa sagittal displacement	-0.1	-0.64, 0.44	0.72	1.4	-
34	Elfeky 2018*	Glenoid fossa sagittal displacement	-0.55	-1.17, 0.07	0.08	2.39	No
35	Croft 1999	Glenoid fossa sagittal/vertical displacement	0.7	0.19, 1.21	0.007	1.2	No
36	Elfeky 2018*	Glenoid fossa transverse displacement	0.41	-0.51, 1.33	0.38	1.68	-
37	Croft 1999	Glenoid fossa vertical displacement	-0.2	-0.85, 0.45	0.55	1.3	-
38	Elfeky 2018*	Glenoid fossa vertical displacement	-0.45	-0.80, -0.10	0.01	0.47	No
39	Arici 2008	Glenoid fossa volume	8	-1.48, 17.48	0.1	90	-
40	Arat 2001	Medial angle (PC as reference)	1.25	-2.86, 5.36	0.55	3.86	-
41	Elfeky 2018*	Medial joint space	-0.67	-0.89, -0.45	<0.001	1	No
42	Chavan 2014	Posterior angle (Bionator; PC as reference)	-13.8	-20.64, -6.96	<0.001	9.9	Yes
43	Chintakanon 1999; 2000	Posterior angle (FH as reference)	3.2	-2.38, 8.78	0.26	11.6	-
44	Arat 2001	Posterior angle (PC as reference)	-2.21	-5.13, 0.71	0.14	2.58	-
45	Chintakanon 1999; 2000	Posterior angle (PC as reference)	-4	-12.08, 4.08	0.33	12.9	-
46	Chavan 2014	Posterior angle (Twin Block/Bionator; PC as reference)	-15.3	-19.70, -10.90	<0.001	9.9	Yes
47	Chavan 2014	Posterior angle (Twin Block; PC as reference)	-16.8	-22.47, -11.13	<0.001	9.9	Yes
48	Arat 2001	Posterior joint space	1.01	0.83, 1.19	<0.001	0.24	Yes
49	Elfeky 2018*	Posterior joint space	1.12	0.73, 1.51	<0.001	0.67	No
50	Arici 2008	Posterior joint space volume	-16	-24.04, -7.96	<0.001	43	No
51	Franco 2002*	Sagittal concentricity	-10.73	-13.03, -8.44	<0.001	3.72	Yes
52	Chavan 2014	Sagittal concentricity (Bionator)	11.55	7.15, 15.95	<0.001	5.1	Yes
53	Chavan 2014	Sagittal concentricity (Twin Block)	15.18	10.28, 20.08	<0.001	5.1	Yes
54	Chavan 2014	Sagittal concentricity (Twin Block/Bionator)	13.37	10.06, 16.68	<0.001	5.1	Yes
55	Arat 2001	Superior joint space	0.64	0.35, 0.93	<0.001	0.31	Yes
56	Elfeky 2018*	Superior joint space	0.89	0.45, 1.33	<0.001	0.76	No

*separate measurements for right and left TMJs were given—the left one was taken in random.

Appendix 5. Detailed assessment of the quality from performed meta-analyses according to the GRADE approach used to construct Table 4.

Outcome	RoB	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect
Anterior joint space	**Serious**	**Ok**	**No**	**Ok**	**NA**	**Yes†**
Posterior joint space	**Serious**	**Ok**	**No**	**Ok**	**NA**	**Yes†**
Superior joint space	**Serious**	**Ok**	**No**	**Ok**	**NA**	**Yes†**
Anterior angle	**Serious**	**Ok**	**No**	**Serious**	**NA**	**No**
Posterior angle	**Serious**	**Ok**	**Mild***	**Serious**	**NA**	**Yes†**
Condylar coronary width	**Serious**	**Ok**	**Mild***	**Serious**	**NA**	**No**
GleFo sagittal displacement	**Serious**	**Ok**	**No**	**Ok**	**NA**	**No**
GleFo vertical displacement	**Serious**	**Ok**	**No**	**Ok**	**NA**	**No**
Sagittal concentricity index	**Serious**	**Ok**	**Serious**	**Serious**	**NA**	**No**

* heterogeneity is high, but all studies are on the same side of the forest plot—i.e. heterogeneity affects only the precise quantification of the treatment effects, but not the decision whether treatment is effective or not.

† Large or very large effect magnitude is seen, but quality of evidence is not upgraded due to existing methodological limitations/risk of bias